REMARKS

I. Introduction

It is respectfully requested that this Amendment After Final Rejection be entered and made of record. It is believed that the following amendments and remarks place the application in a form for allowance. The following amendments and remarks at least place the claims in a better form for appeal. No new matter is presented, as such the amendment is proper under 37 C.F.R. § 1.116.

II. Claim Rejections - 35 U.S.C. § 112

Claims 1, 3, 5, 6, 9-11, 15, and 16 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner has objected to the recitation that the peptide, oligopeptide or protein is administered in a dose of "from about 20-500 μg/kg."

Applicants have now amended independent claims 1, 10, and 16 to specify that the compound is administered "intravenously". Since the Examiner notes that the original specification supports administration of compound in this dosing range intravenously, it is respectfully submitted that this ground of rejection is rendered moot.

III. Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 1, 3, 5, 6, 9-11, 13, 15, and 16 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner first states that the specification has differing meanings for the term "peptide". Specifically, the Examiner states that in claims 3 and 13, "peptide" does not accurately characterize L-arginine. Applicant has now amended claims 3 and 13, as well as independent claims 1, 10, and 16, to provide that the method involves administering to the mammal a peptide, oligopeptide, protein or L-arginine. Literal support for this claim amendment is found on page 7 of the specification, lines 17-18. No new matter has been added. Thus, it is respectfully submitted that this discrepancy has been alleviated.

Second, the Examiner states that the recitation of "[Lys]-BK" in claims 3 and 13 is confusing. Accordingly, Applicants have now deleted this term and substituted "SEQ ID NO:7", as shown in the specification on page 16. No new matter has been added. Claims 3 and 13 have also been amended to remove the other abbreviations the Examiner states are unclear and replace them with the appropriate SEQ ID numbers shown on page 16.

Next, the Examiner states that claims 3 and 13 are indefinite on the basis that the term "polyarginine" does not designate a specific compound without an indication of molecular weight. Accordingly, claims 3 and 13 have been amended to designate that the polyarginine has a molecular weight of 5,000, as set forth in Table 1.

Finally, the Examiner states that claims 3 and 13 do not further limit the independent claim on the basis that BK fragment 2-7 has no arginine as required by the independent claim and that the arginine in Met-Lys-BK is not accessible to NO synthase as shown in Table 1. Applicants have now amended claims 3 and 13 to replace "BK fragment 2-7" with the SEQ ID NO. for BK fragment 1-5 which does include an arginine. "Met-Lys-BK" has been deleted from claims 3 and 13.

IV. Claim Rejections - 35 U.S.C. § 102(b)

A. Groves et al.

Claims 1, 5, 6, 10, 11, 15, and 16 were rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Groves et al. The Examiner argues that Groves et al. teach Applicants' one-step method of the administration of a regulator of NO production, HOE-140, a bradykinin antagonist to a human. Applicants respectfully traverse this rejection.

Applicants have now amended independent claims 1, 10, and 16 to specify that Applicants' method involves the stimulation or inhibition of nitric oxide synthase. The Examiner acknowledges the statement in Groves that "HOE-140 had no influence on NO synthase activity in cultured endothelial cells implies that is effects were not attributable to a nonspecific inhibition of enzymatic NO formation." However, the Examiner surmises that the effect of HOE-140 in vivo may have been as a specific inhibitor of NO formation. Regardless of whether the Examiner's hypothesis is true, the fact remains that Groves does not disclose or teach Applicants' claimed invention, namely stimulation or inhibition of nitric oxide synthase since it specifically states that HOE-140 "had no influence on NO synthase activity."!

As discussed in Applicants' last response, an anticipatory reference must generally place the needed subject matter supporting the anticipation rejection in the public domain before the date of the invention. In re Zenitz, 333 F.2d 924 (CCPA 1964). It therefore follows that a reference does not legally anticipate the claimed subject matter if it is found not to be sufficiently enabling, in other words, if it does not place the subject matter of the claims within the possession of the public. In re Wilder, 429 F.2d 447 (CCPA 1970).

Here, there can be no dispute but that Groves does not place the subject matter of the claimed invention in the possession of the public, especially since its conclusions directly

contradict the method of Applicants' claims. A person skilled in the art at the time of Applicants' invention would not have realized from the teachings of Groves that an arginine-rich peptide, oligopeptide, or protein would be effective in stimulating or inhibiting nitric oxide synthase. Thus, claims 1, 5, 9-11, 15, and 16 are not anticipated by Groves et al.

Applicants would also note that claim 16 provides that the peptide, oligopeptide, or protein is selected from the group consisting of the compounds listed in Table 1. Since Groves et al. do not disclose or teach the use of any of these compounds, it is respectfully submitted that claim 16 is not anticipated by Groves et al.

Claims 1, 5, 9-11, 16, and 16 are also not rendered obvious by Groves. There is no teaching or suggestion in Groves to administer an arginine-rich peptide, oligopeptide, or protein to stimulate or inhibit NO synthase, especially in view of the fact that Groves et al. teach exactly the opposite.

B. Thiemermann et al.

Claims 1, 5, 9-11, 15, and 16 were rejected under 35 U.S.C. § 102(b) as being anticipated by Thiemermann et al. The Examiner argues that Thiemermann's disclosure of the administration of 1-30 mg/kg of NO_2-Arg-L-arginine and other dipeptides containing arginine, in vivo, to rats for the purpose of raising blood pressure anticipates Applicants' one-step method of administering a peptide, oligopeptide, or protein to a mammal in order to regulate NO production.

As with the Groves reference, Thiemerman et al. do not teach Applicants' claimed method of administering an arginine-rich compound in order to stimulate or inhibit NO synthase. A person skilled in the art at the time of Applicants' invention would not have realized from the teachings of Thiermerman et al. that an arginine-rich peptide, oligopeptide, or protein would be

effective in stimulating or inhibiting nitric oxide synthase. Thus, claims 1, 5, 9-11, 15, and 16 are not anticipated by Thiermerman et al.

Applicants would again note that claim 16 provides that the peptide, oligopeptide, or protein is selected from the group consisting of the compounds listed in Table 1. Since Thiemerman et al. do not disclose or teach the use of any of these compounds, it is respectfully submitted that claim 16 is not anticipated by Thiermerman et al.

Claims 1, 5, 9-11, 15, and 16 are also not rendered obvious by Thiermerman et al. There is no teaching or suggestion in Thiermerman et al. to administer an arginine-rich peptide, oligopeptide, or protein to stimulate or inhibit NO synthase.

C. Pang et al.

Claims 1, 2, 5, 6, 10, 11, 15, and 16 were rejected under 35 U.S.C. § 102(b) as being anticipated by Pang et al., U.S. Patent No. 4,585,757. The Examiner notes that Pang et al. discloses the administration of arginine containing peptides CIP fragment and contraceptive tetrapeptide in the rage of 50-500 micrograms/kg to lower blood pressure.

Pang et al. also do not teach Applicants' claimed method of administering an arginine-rich compound in order to stimulate or inhibit NO synthase. A person skilled in the art at the time of Applicants' invention would not have realized from the teachings of Pang et al. that an arginine-rich peptide, oligopeptide, or protein would be effective in stimulating or inhibiting nitric oxide synthase. Thus, claims 1, 2, 5, 6, 10, 11, 15, and 16 are not anticipated by Pang et al.

Further, claim 16 provides that the peptide, oligopeptide, or protein is selected from the group consisting of the compounds listed in Table 1. Since Pang et al. do not disclose or teach the use of any of these compounds, it is respectfully submitted that claim 16 is not anticipated by Pang et al.

Claims 1, 2, 5, 6, 10, 11, 15, and 16 are also not rendered obvious by Pang et al. There is no teaching or suggestion in Pang et al. to administer an arginine-rich peptide, oligopeptide, or protein to stimulate or inhibit NO synthase.

V. Claim Rejections – 35 U.S.C. § 103(a)

Claims 1, 3, 5, 6, 9-11, 13, 15, and 16 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Dietze et al., U.S. Patent No. 4,152,425. The Examiner argues that the use of up to 3000 μg of kinin/l solution as described in Dietze et al. renders the claimed invention obvious. Claims 1, 5, 6, 9-11, 15, and 16 were also rejected under 35 U.S.C. § 103(a) as being obvious over Henke et al., U.S. Pat. No. 5,648,333. With respect to this reference, the Examiner argues that the administration of the various peptides which are bradykinin antagonists in the range of 10μg-10mg/kg renders the claimed invention obvious.

Dietze et al. teach the infusion of a glucose-containing infusion solution that is especially useful for intravenous feeding. (Col. 2, lines 5-7). The solution comprises glucose and at least one kinin. (Col. 2, lines 7-10). Henke et al. teach novel peptides having bradykinin antagonist action. As acknowledged by the Examiner, there is no discussion whatsoever, in Dietze et al. or Henke et al. regarding the use of bradykinin or other arginine-containing peptides on NO production and/or stimulating or inhibiting NO synthase. The Examiner, however, argues that although the references are silent with regard to the effects of the administration of bradykinin or arginine containing peptides on NO production, "it is reasonable to assume that the effects would be the same as claimed because, the patient is the same, the compounds administered are the same, the dosage is the same, the mode of administration is the same; therefore, the results would inherently be the same." Specifically, the Examiner states that if the active step of the method is the same and the subject is the same, "then the claimed method can be anticipated or made

obvious by the prior art, even if the prior art does not recognize or appreciate this mechanism as long as the compound administered, dosage, mode of administration, subject, etc. are the same as in the method disclosed in the prior art." (Office Action, p. 7). Applicants respectfully traverse this rejection.

The Examiner is apparently stating that it is not possible for Applicants to obtain a patent pertaining to the administration of a known compound in a known dose range for a new purpose since the previous administration of this compound as described in the prior art would have inherently provided the applicants' newly claimed, never-before realized effect on the body. However, if this was the law, how is it possible that patents issued on both inventions described by Denske et al. and Henske et al., which both describe the administration of an arginine-containing compound in the same dose ranges?

Further, Applicants hereby draw the following patents pertaining to the administration of fluoxetine to the Examiner's attention:

-U.S. Pat. No. 5,962,463 (Nitsch et al.) directed to a method of preventing, delaying or reducing the formation of amyloid plaques deposited in the brain by administering fluoxetine (no required dose level)(see claim 1);

-U.S. Pat. No. 5,985,322 (Anderson et al.) directed to a method of treating depression, obsessive-compulsive disorder, bulimia, pain, post-traumatic stress disorder, obsessive-compulsive personality disorder, hypertension, atherosclerosis, anxiety, anorexia nervosa, along with several other disorders by administering 20-100 mg of fluoxetine (claims 1-2);

-U.S. Pat. No. 6,075,020 (Cincotta et al.) directed to a method of regulating immune function comprising administering a prolactin enhancer, which may be fluoxetine (no required dose level)(see claim 1); and

-U.S. Pat. No. 6,245,782 (Serebruary et al.) directed to a method of inhibiting platelet activation with selective serotonin reuptake inhibitors, which may be fluoxetine in a dose of from 10-2500 mg daily (see claim 1).

Thus, at least four separate patents have issued on the one-step process of administering fluoxetine in the same dose ranges for treating different disease states and conditions. In accordance with the Examiner's theory, these patents could not have all issued since administering fluoxetine in the overlapping doses described (and omitted in the claims) would inherently result in the treatment of all of the claimed disorders of these patents. Thus, the first-issued patent would have foreclosed the issuance of any other method patents describing the administration of fluoxetine for any purpose. Obviously, such is not the case since the law provides that patents may issue on methods of treatment of various diseases through the same or different pathways so long as the prior art does not teach or suggest the use of such composition such as to enable persons skilled in the art to practice the claimed invention, as extensively shown above. Thus, the Examiner's obviousness rejection must fail as a matter of law, and Applicants respectfully request that these grounds of rejection be withdrawn.

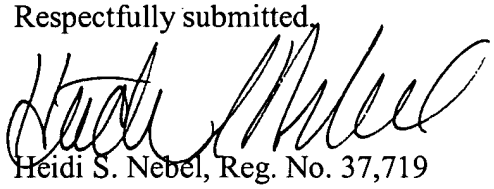
VI. Conclusion

It is believed the application is in a prima facie condition for allowance. Allowance is respectfully requested.

No fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,



Heidi S. Nebel, Reg. No. 37,719
ZARLEY, McKEE, THOMTE, VOORHEES
& SEASE
801 Grand Avenue, Suite 3200
Des Moines, Iowa 50309-2721
Phone No. (515) 288-3667
Fax No. (515) 288-1338
CUSTOMER NO: 22885

Attorneys of Record

- wm -

AMENDMENT — VERSION WITH MARKINGS TO SHOW CHANGES MADE — DO NOT FILE

In the Claims

Claims 1, 3, 10, 13, and 16 were amended as follows:

1. (Twice Amended)

A method of [regulating or controlling nitric oxide production] stimulating or inhibiting nitric oxide synthase for the prevention or treatment of certain nitric oxide-mediated pathogenic conditions in a mammalian subject comprising intravenously administering to the mammal from about 20-500 μg/kg of a peptide, oligopeptide, [or] protein, or L-arginine that acts as a substrate for or an inhibitor of nitric oxide synthase, whereby the tertiary structure of the peptide, oligopeptide, or protein inhibitor is such that one or more arginine groups are available to the nitric oxide synthase.

3. (Twice Amended)

The method of claim 1, wherein the peptide, oligopeptide, [or] protein or L-arginine is selected from the group consisting of L-Arginine, Poly-Arginine (M_r 5,000), [BK] SEQ ID NO:1, [Des-Arg1-BK] SEQ ID NO:2, [Des-Arg9-BK] SEQ ID NO:3, [BK fragment 1-7] SEQ ID NO:4, [BK fragment 2-7] SEQ ID NO:5, [[Lys1]-BK] SEQ ID NO:7, [Lys-BK] SEQ ID NO:8, and [Ile-Ser-BK] SEQ ID NO:9[, and Met-Lys-BK].

10. (Twice Amended)

A method of preventing or treating a [nitric oxide-mediated] disease or condition in a mammalian subject that is affected by stimulation or inhibition of nitric oxide synthase

comprising intravenously administering to the subject in need of such prevention or treatment from about 20-500 μg/kg of a peptide, oligopeptide, [or] protein or L-arginine that acts as a substrate for or an inhibitor of nitric oxide synthase.

13. (Amended)

The method of claim 10, wherein the peptide, oligopeptide, [or] protein or L-arginine is selected from the group consisting of L-Arginine, Poly-Arginine (M_r 5,000), [BK] SEQ ID NO:1, [Des-Arg1-BK] SEQ ID NO:2, [Des-Arg9-BK] SEQ ID NO:3, [BK fragment 1-7] SEQ ID NO:4, [BK fragment 2-7] SEQ ID NO:5, [[Lys1]-BK] SEQ ID NO:7, [Lys-BK] SEQ ID NO:8, and [Ile-Ser-BK] SEQ ID NO:9[, and Met-Lys-BK].

16. (Amended)

A method of [regulating or controlling nitric oxide production] stimulating or inhibiting nitric oxide synthase for the prevention or treatment of certain nitric oxide-mediated pathogenic conditions in a mammalian subject comprising intravenously administering to the mammal from about 20-500 μg/kg of a peptide, oligopeptide, [or] protein or L-arginine that acts as a substrate for a nitric oxide synthase, whereby the tertiary structure of the peptide, oligopeptide, or protein inhibitor is such that one or more arginine groups are available to the nitric oxide synthase, said peptide, oligopeptide or protein being selected from the group consisting of L-Arginine, Poly-Arginine (M_r 5,000), [BK] SEQ ID NO:1, [Des-Arg1-BK] SEQ ID NO:2, [Des-Arg9-BK] SEQ ID NO:3, [BK fragment 1-7] SEQ ID NO:4, [BK fragment 2-7] SEQ ID NO:5, [[Lys1]-BK] SEQ ID NO:7, [Lys-BK] SEQ ID NO:8, and [Ile-Ser-BK] SEQ ID NO:9[, and Met-Lys-BK].